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Skeletal Muscle as a Dynamic Organ that Orchestrates Whole Body Metabolism

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Disclosures

- Danone – Advisory Board
- Smartfish – Research Collaboration
- Abbott Nutrition – Research Collaboration
- Rottapharm – Advisory Board
- Acacia – Research Collaboration
- Santhera – Research Collaboration

Learning Objectives

1. Provide an overview of the relationship between skeletal muscle and metabolism

2. Describe skeletal muscle plasticity in response to environmental and physiological challenges

3. Discuss the clinical implications in muscle wasting conditions

The Muscle and Its Main Functions

SKELETAL MUSCLE

JAMDA 17 (2016) 789–796

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JAMDA

journal homepage: www.jamda.com

Review Article

Skeletal Muscle Regulates Metabolism via Interorgan Crosstalk: Roles in Health and Disease

CrossMark

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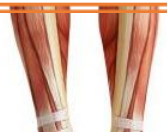
Maintenance of posture and balance



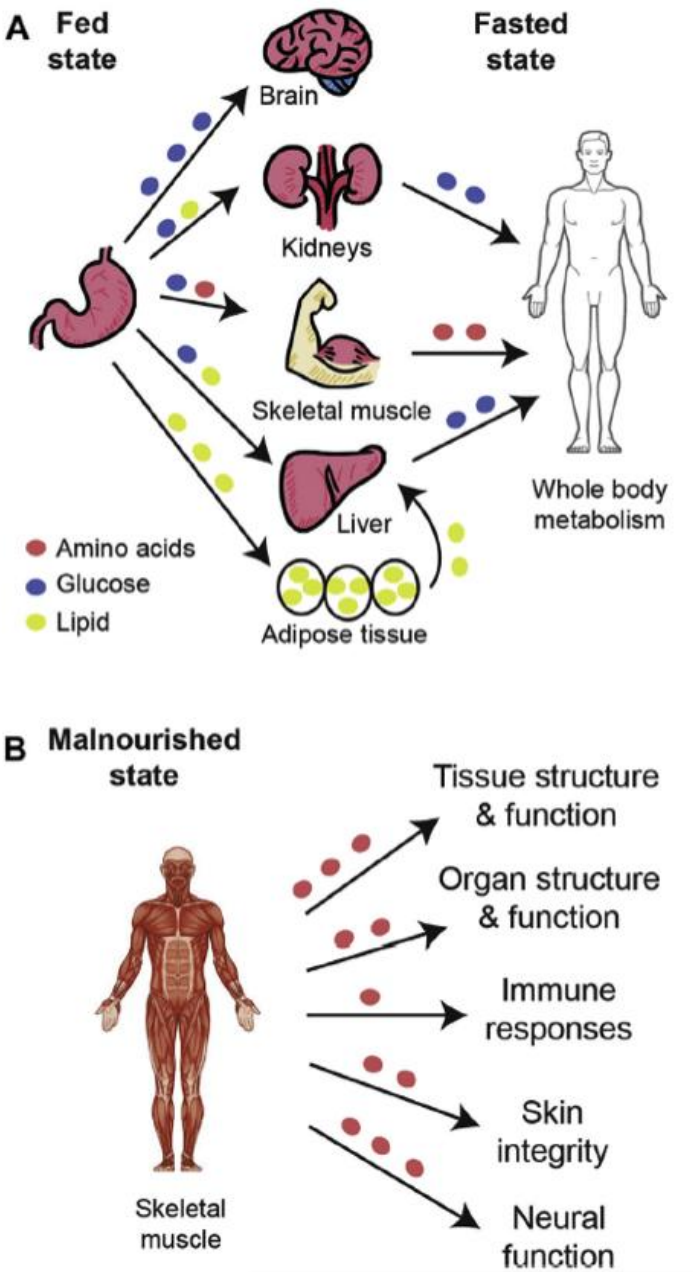
storage

Regulator of glucose levels

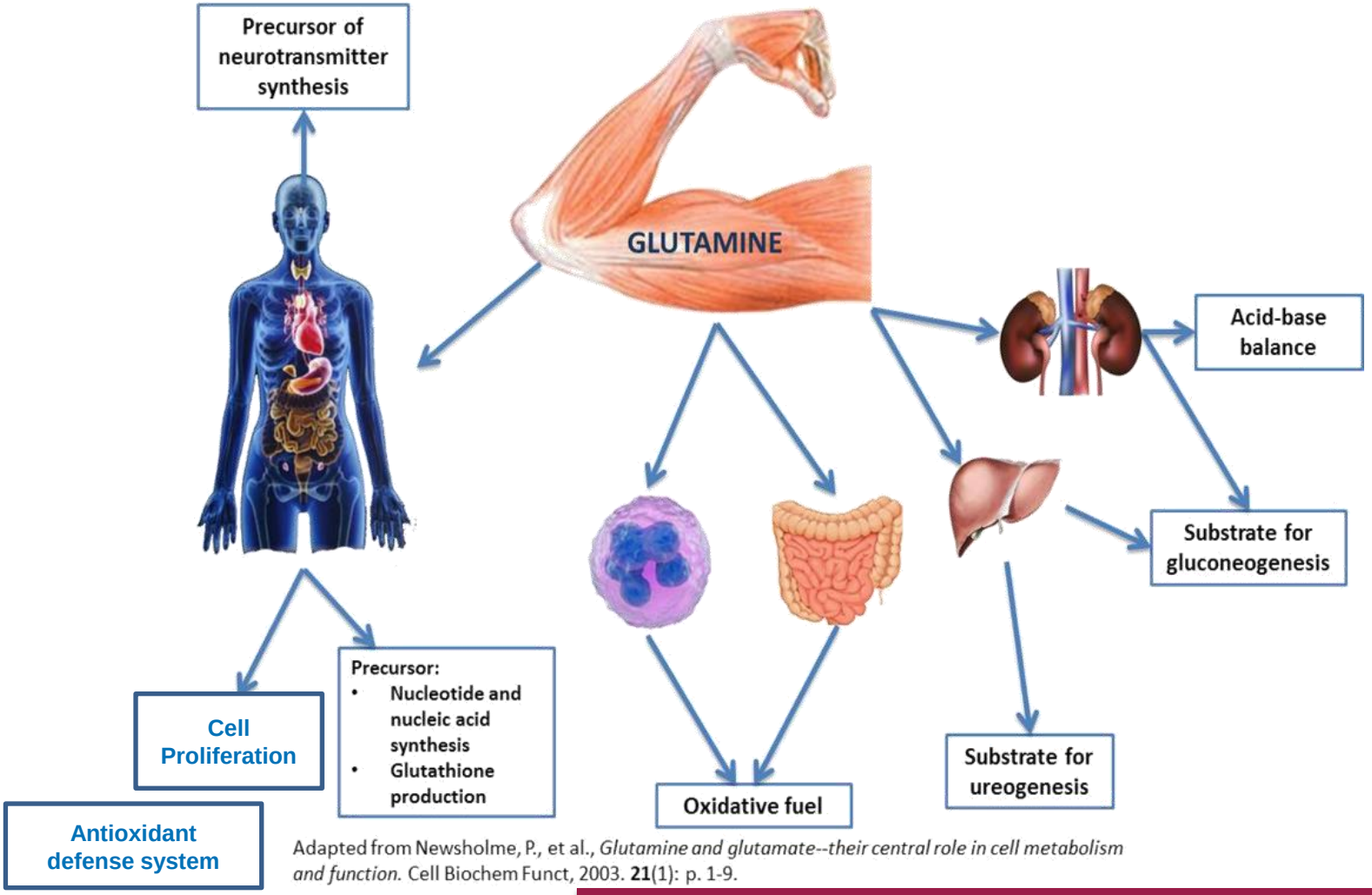
Average Muscle Mass

38-54% men

28-39% women

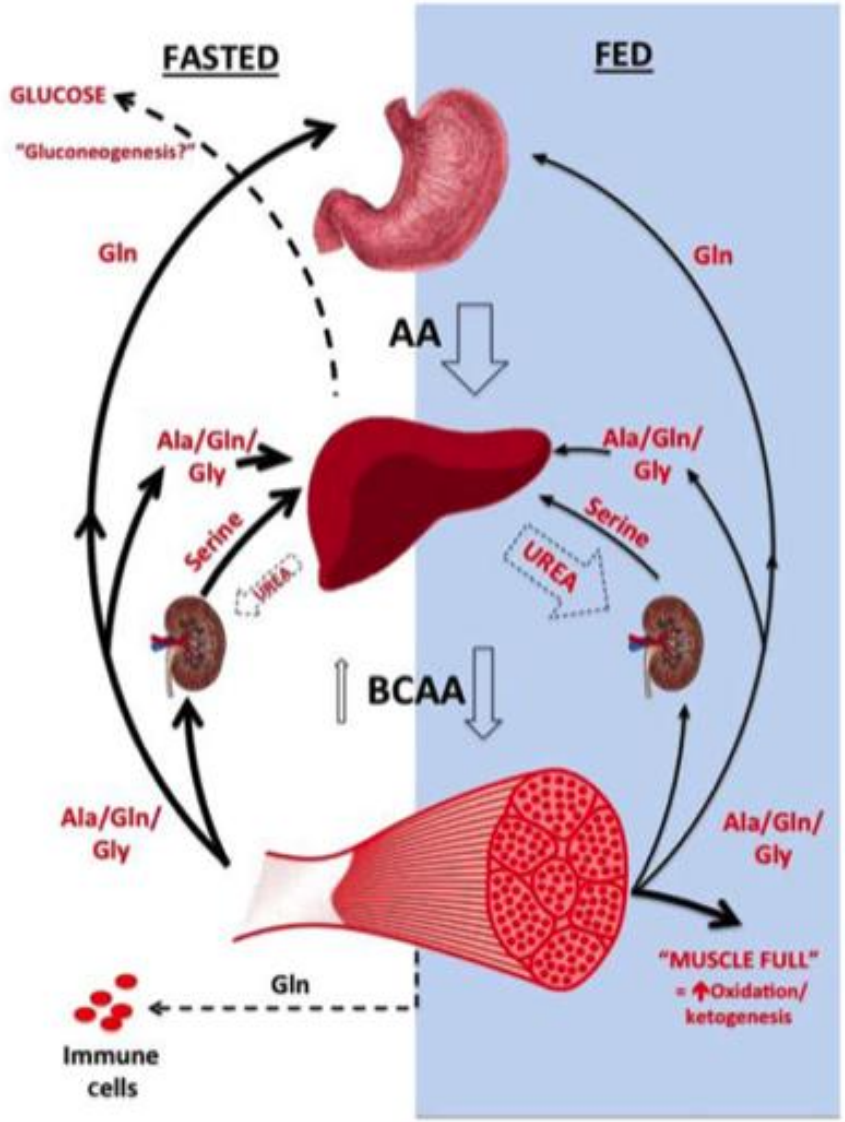

A
Fed state
Fasted state
Brain
Kidneys
Skeletal muscle
Liver
Adipose tissue
Whole body metabolism
Amino acids
Glucose
Lipid
B
Malnourished state
Tissue structure & function
Organ structure & function
Immune responses
Skin integrity
Neural function
Skeletal muscle

Glutamine is Mainly Synthesized and Stored in Skeletal Muscle



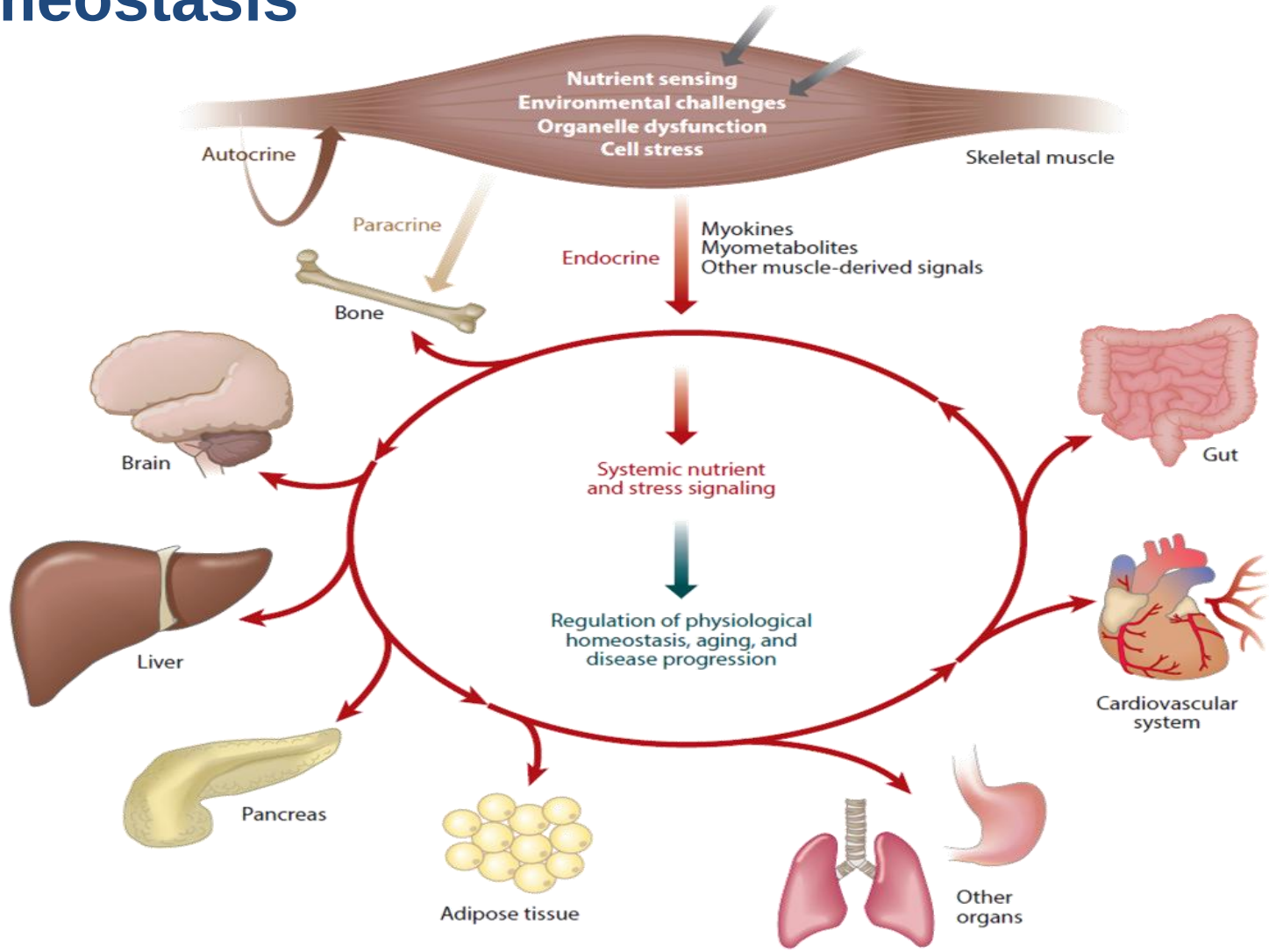
Adapted from Newsholme, P., et al., *Glutamine and glutamate--their central role in cell metabolism and function.* Cell Biochem Funct, 2003. **21**(1): p. 1-9.

Newsholme, P. et al. Cell Biochem. Funct., 2003



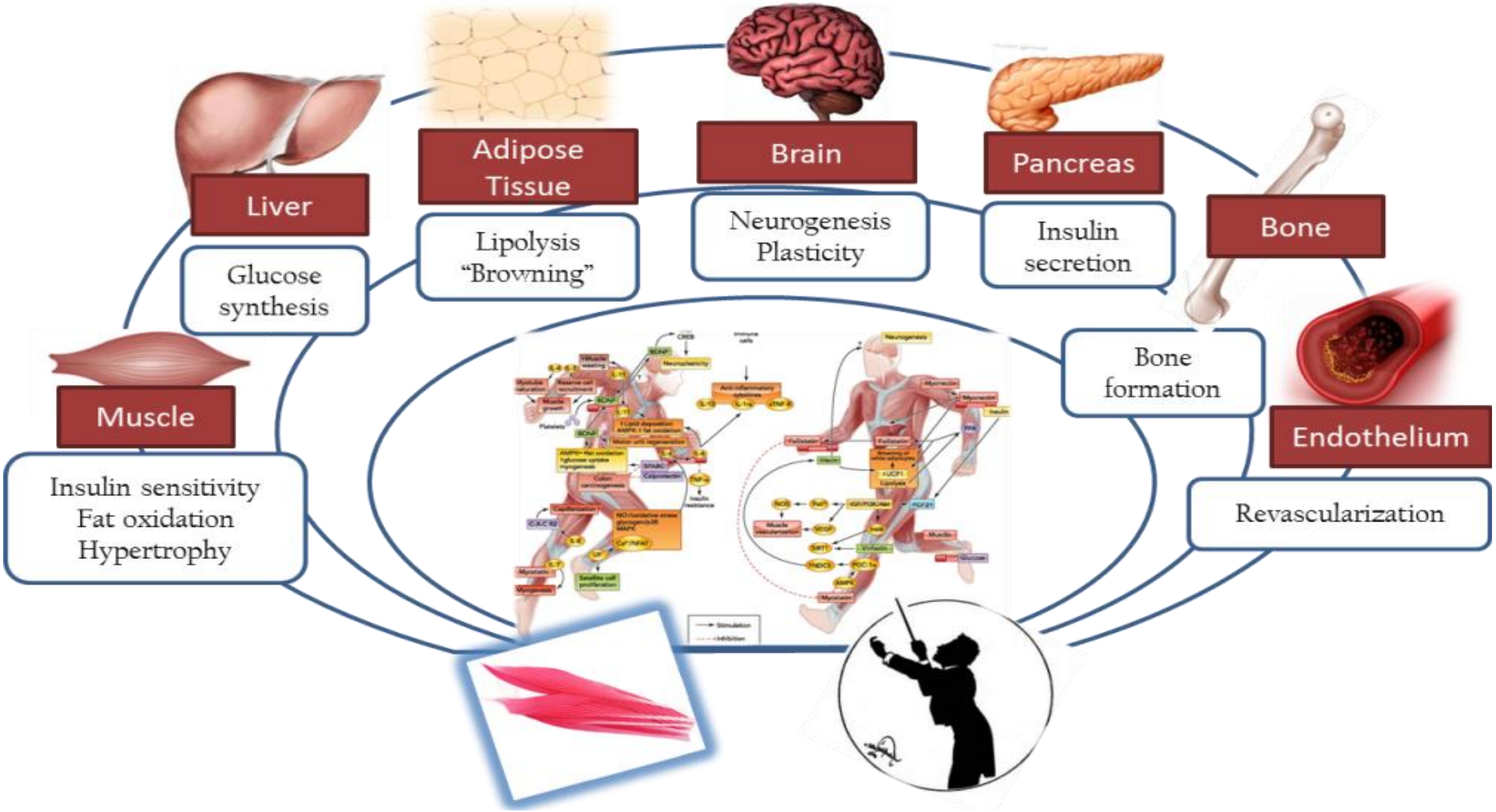
Adapted from Brosnan, J.T., J. Nutr. 2003

Skeletal Muscle is a Regulator of Metabolic Homeostasis



Rai et al (2016) *Annu. Rev. Physiol*. 78:85–107

Skeletal Muscle Orchestrates Metabolic Events



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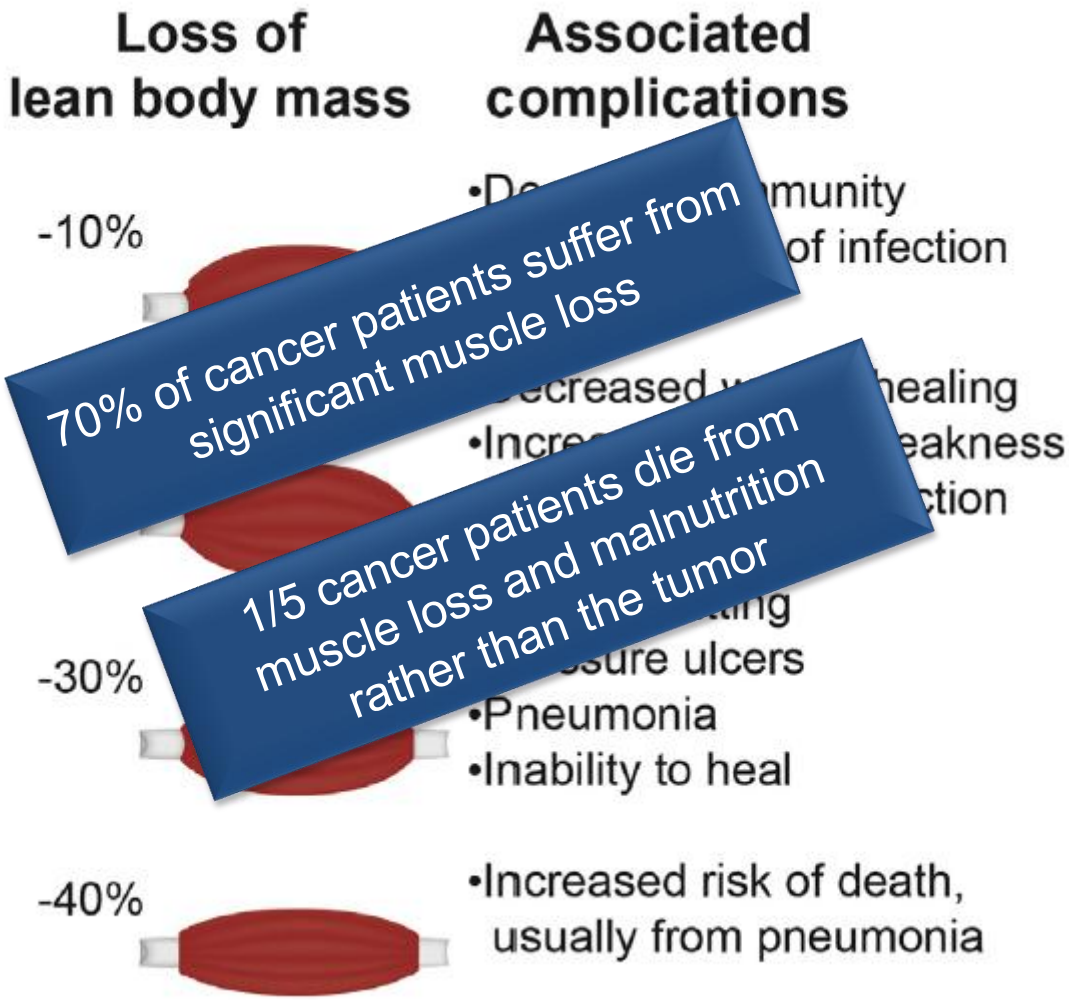
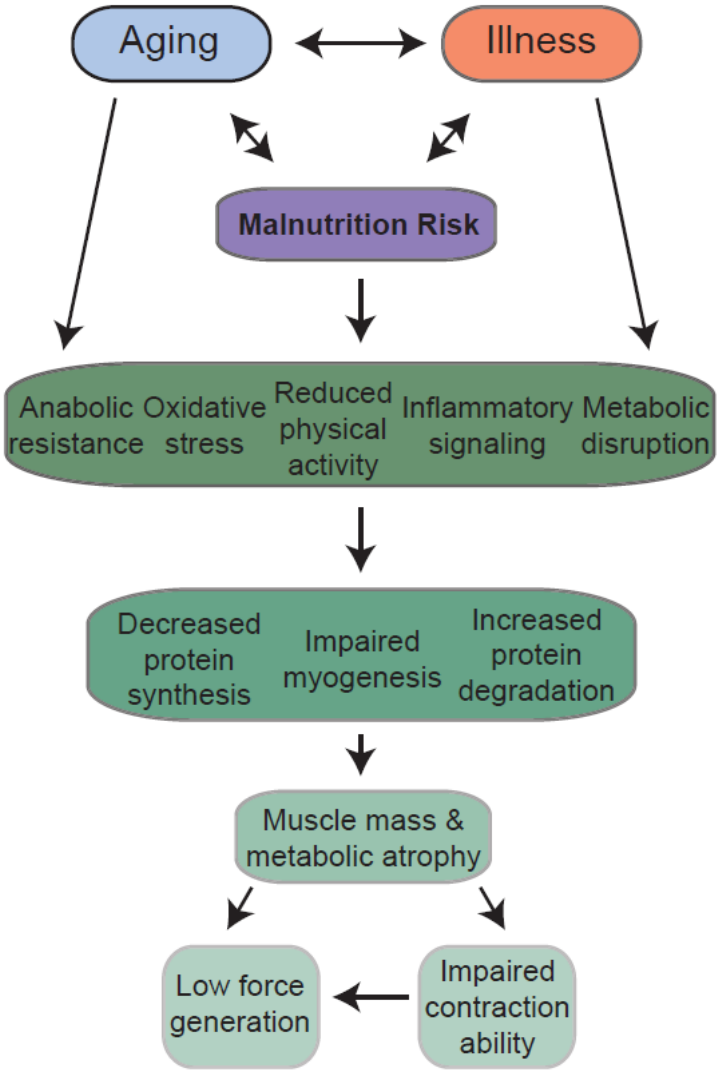
Adapted from Fiuza-Luces C et al (2013) *PHYSIOLOGY* 28: 330–358
Pedersen BK & Febbraio MA (2012) *Nat. Rev. Endocrinol.* 8, 457–465

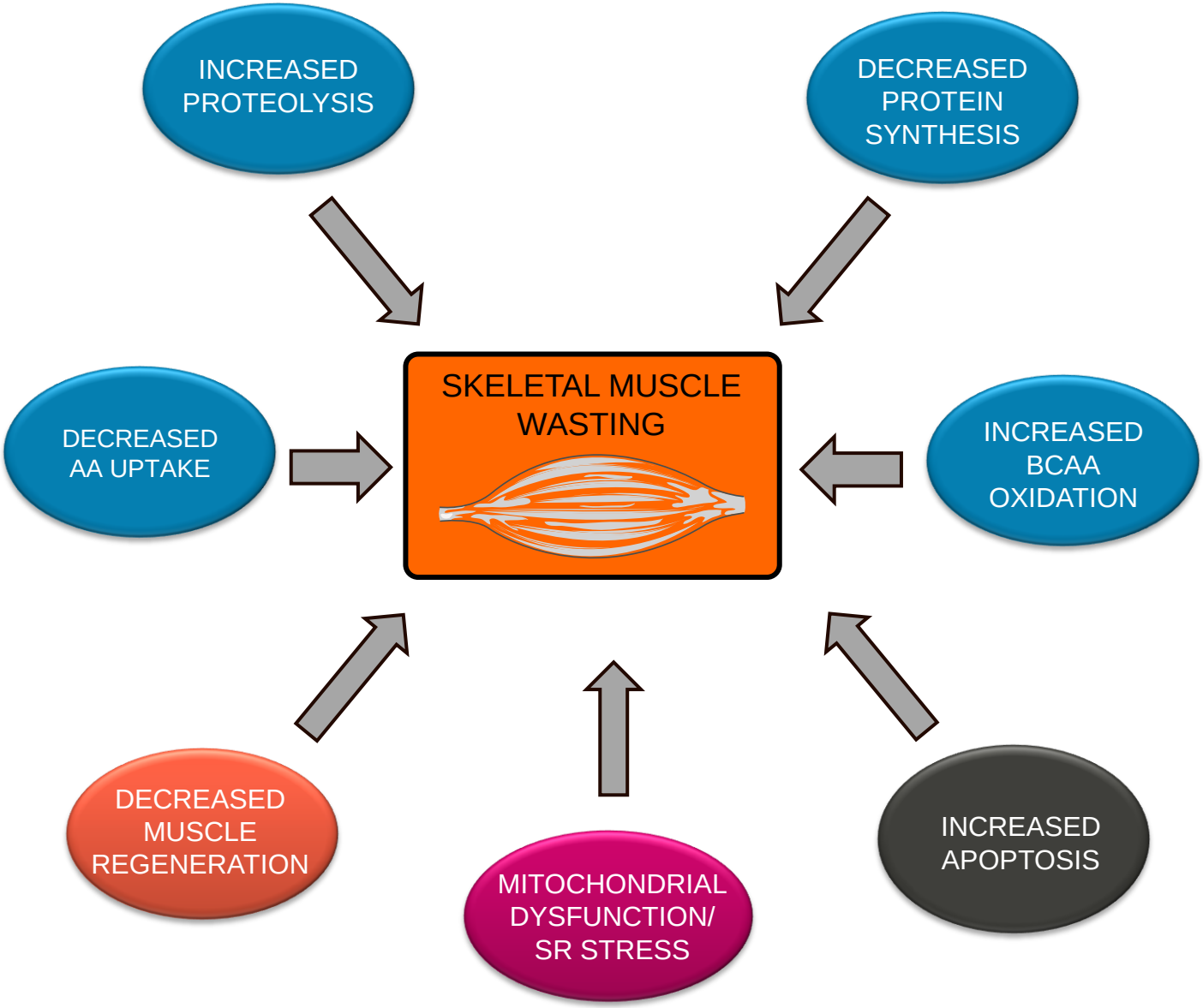
Complications of Lean Body Mass (Muscle) Loss



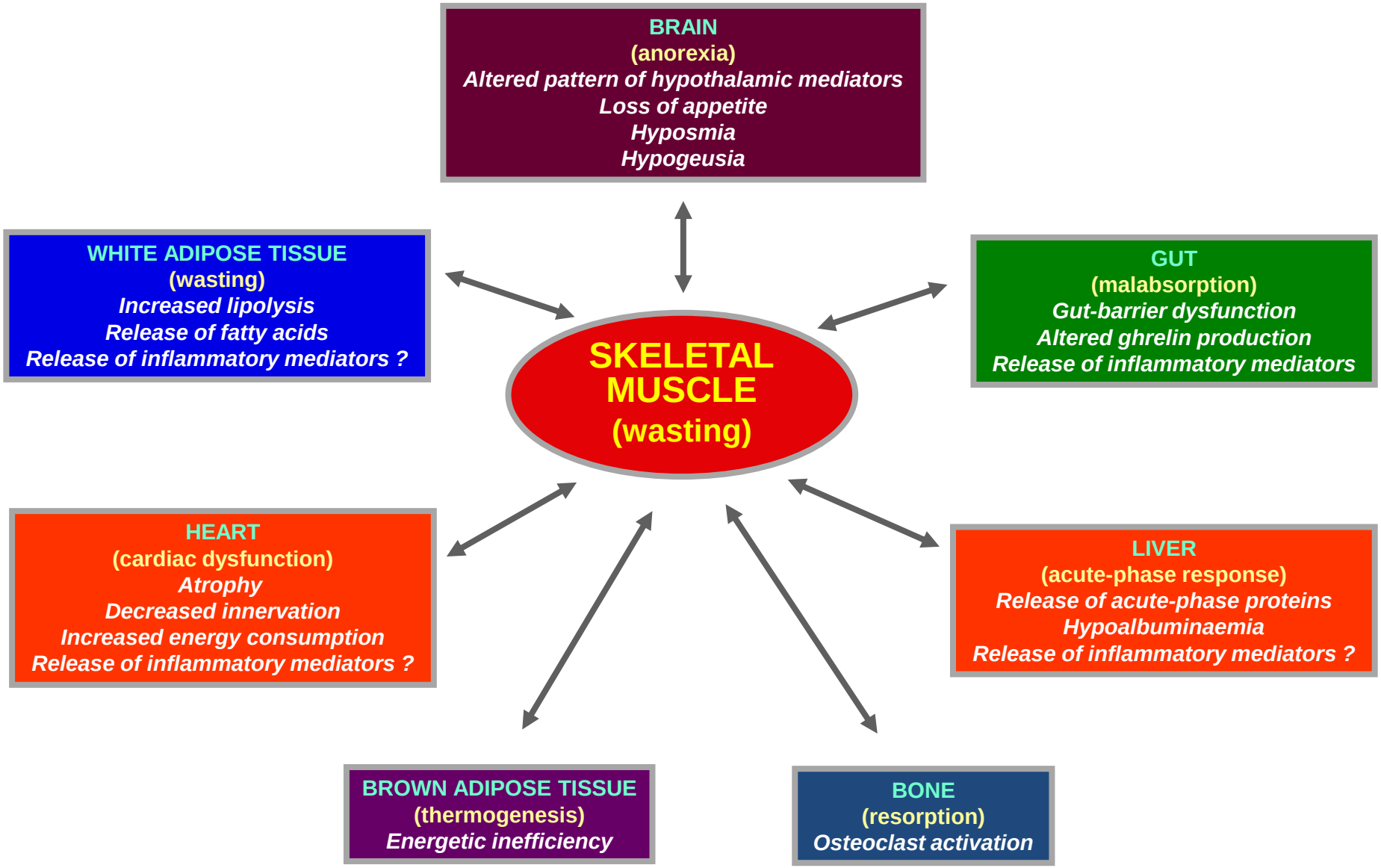
Effects of Ageing and Illness on Muscle Mass



Argilés, J.M. et al. JAMDA, 2016


INCREASED PROTEOLYSIS
DECREASED PROTEIN SYNTHESIS
DECREASED AA UPTAKE
SKELETAL MUSCLE WASTING
INCREASED BCAA OXIDATION
DECREASED MUSCLE REGENERATION
MITOCHONDRIAL DYSFUNCTION/ SR STRESS
INCREASED APOPTOSIS

Skeletal Muscle Wasting Crosstalk



Argilés J.M. et al. Nature Rev. Cancer., 2014

Skeletal Muscle is Not Just Associated with Contraction

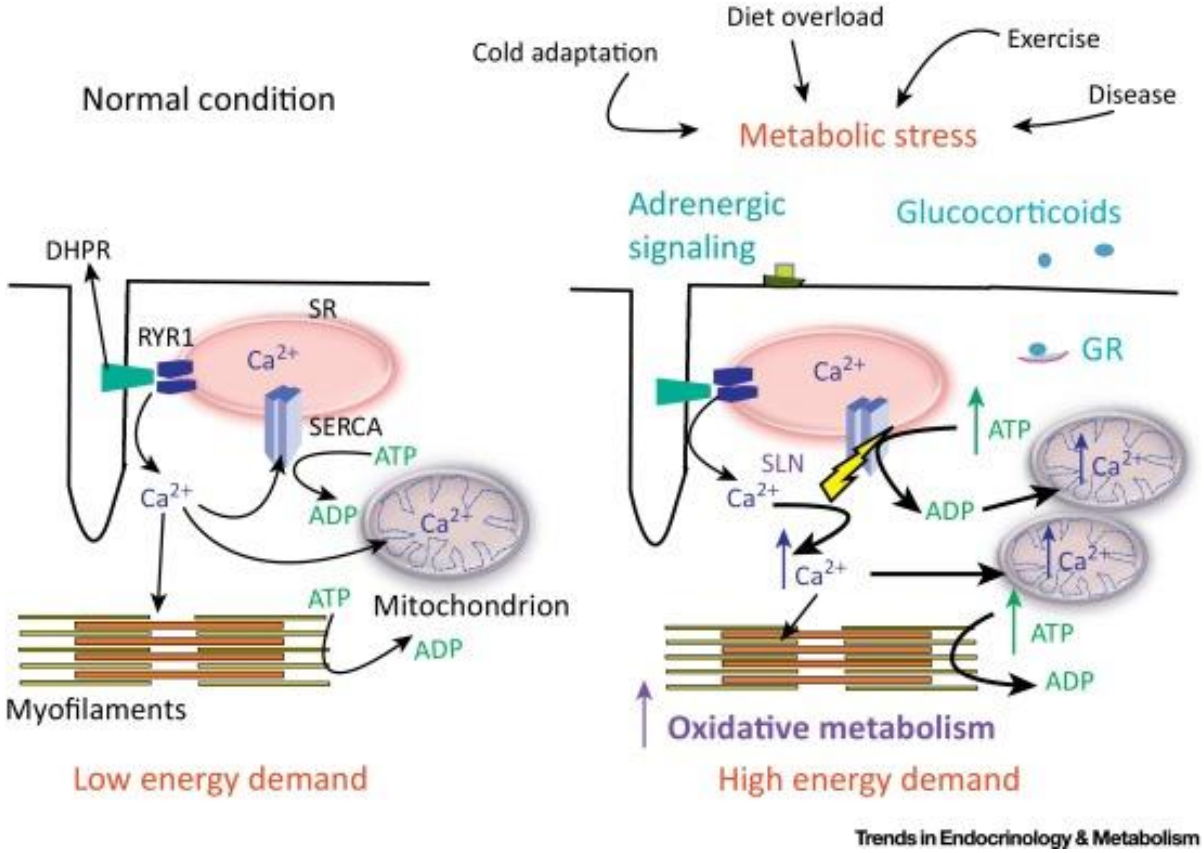
Skeletal muscle as a thermogenic organ

Types of thermogenesis

Shivering

Non-shivering

Sarcolipin: A Key Thermogenic and Metabolic Regulator in Skeletal Muscle

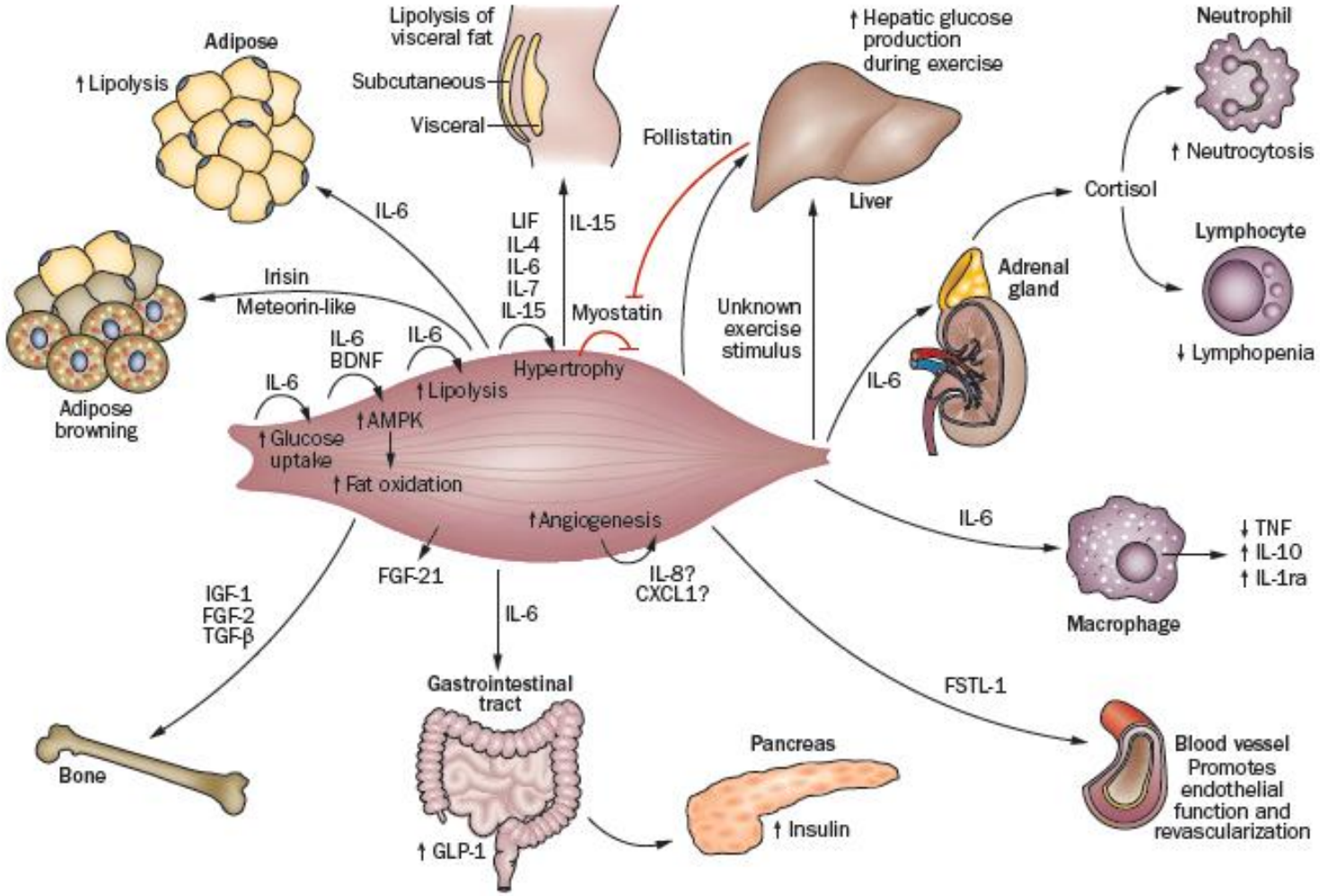


Sarcolipin Promotes Oxidative Metabolism under Conditions of Increased Energy Demand. During muscle contraction, membrane depolarization leads to activation of DHPR/RYR1 complex leading to release of Ca^{2+} from the SR.

Pant, M. et al. Trends Endocrinol. Metabol., 2016

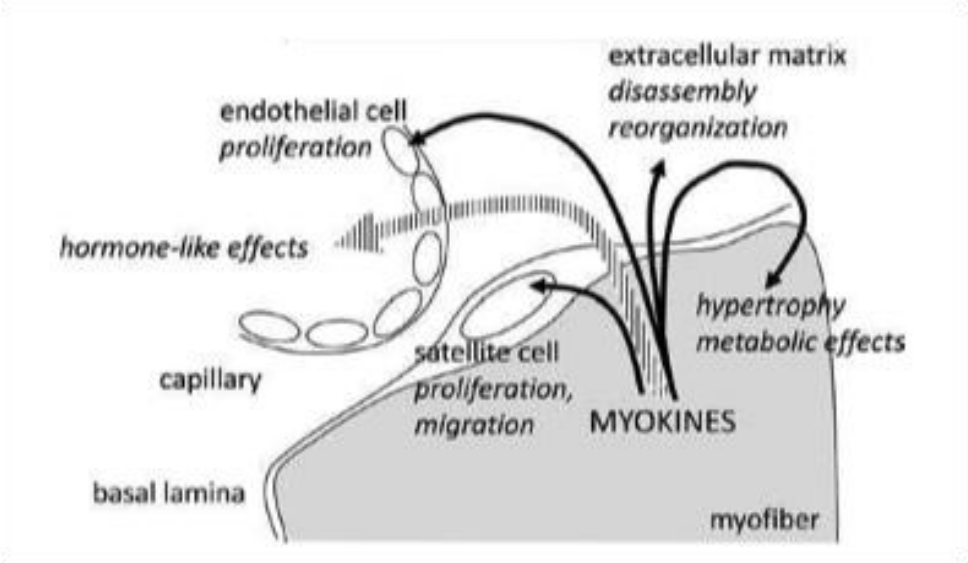
Skeletal Muscle as an Endocrine Tissue

Glucose Metabolism | **Lipid Metabolism** | **Vascular Function** | **Inflammation** | **Brain Function**



Karstoft K & Pedersen BK.
Curr Opin Clin Nutr Metab Care. 2016

Functions of Myokines



Weigert, C. et al. Proteomics Clin. Appl., 2014

How Do We Address the Underlying Metabolic Dysfunction Leading To Muscle Loss?

Muscle Protein Breakdown

Muscle Protein Synthesis

Net Balance

Inflammation

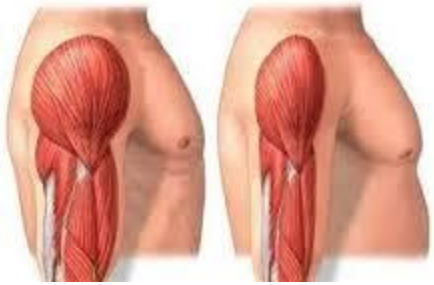
Low anabolic hormones

Insulin resistance

Low blood flow

Drugs?

↑ Muscle Loss



↓ Muscle Gain

DRUGS

DRUGS

DRUGS

DRUGS

DRUGS

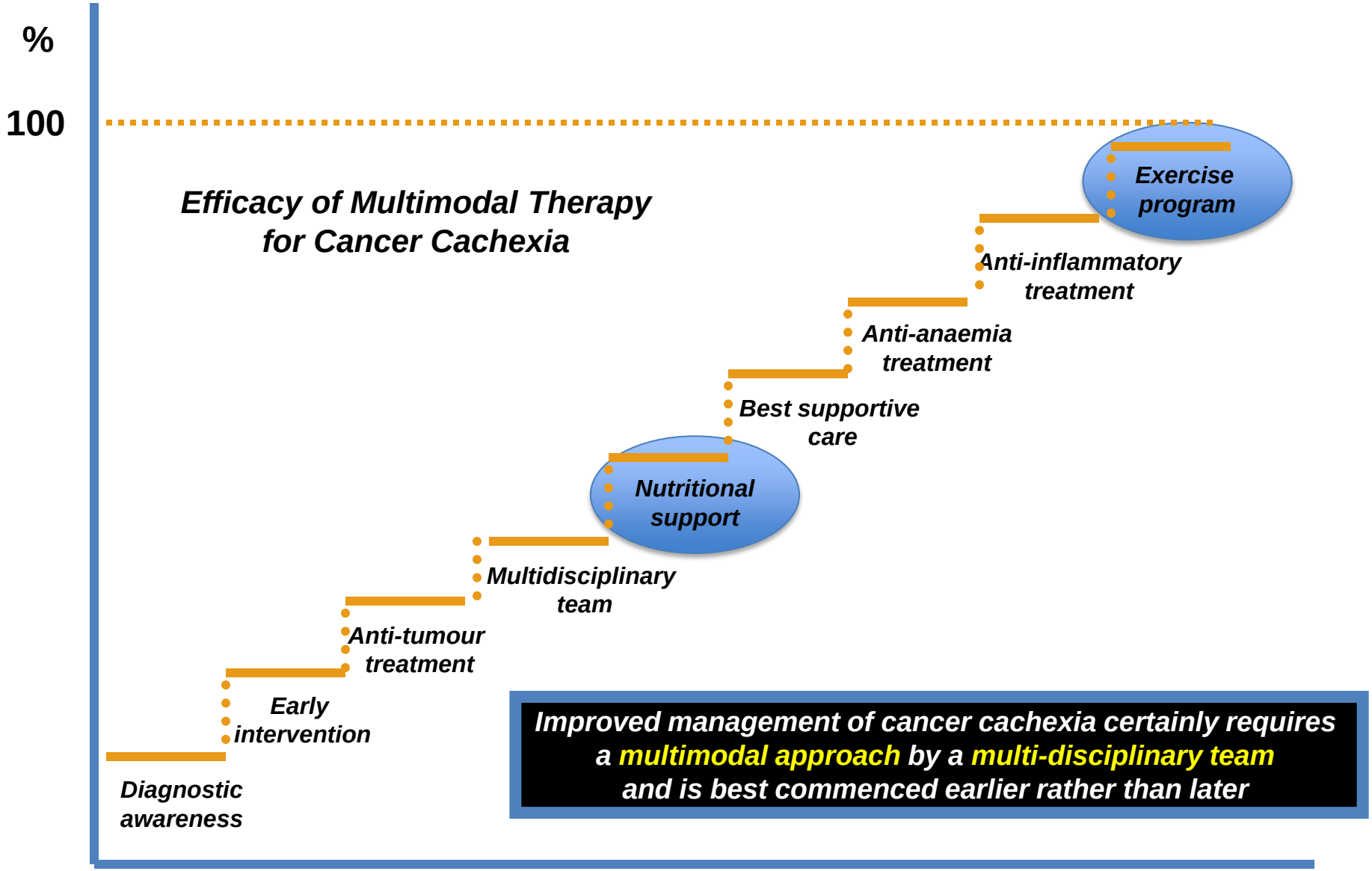
TOXICITY

TOXICITY

TOXICITY

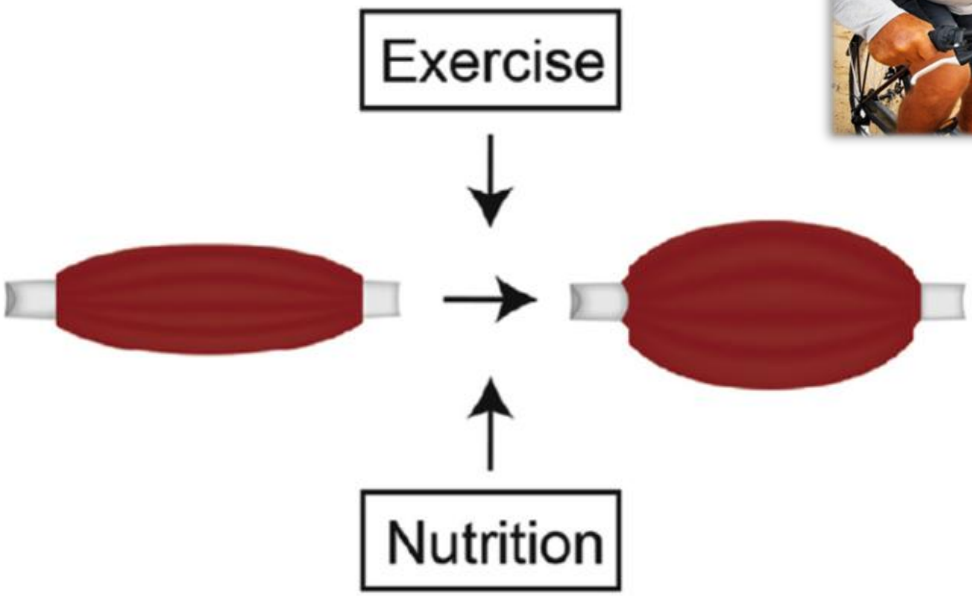
TOXICITY

TOXICITY



Argilés, J.M. et al. Biochem. J., 2017

Physical activity, especially resistance training stimulates protein synthesis in muscle

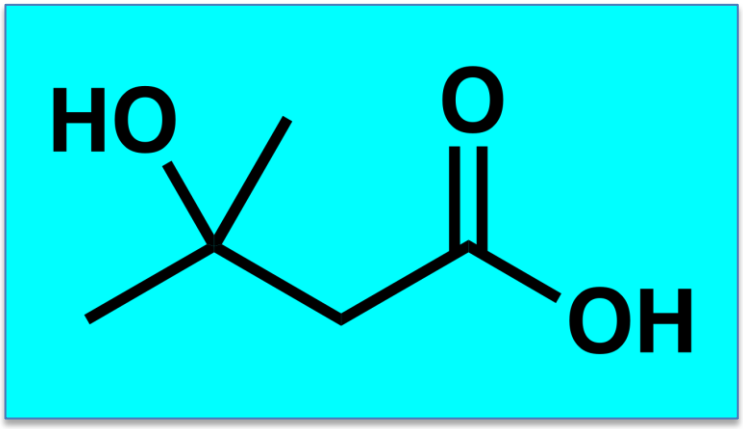


High-protein diets including EAAs and BCAAs contribute to muscle accretion

The leucine metabolite HMB is a potent stimulator of protein synthesis in muscle

Argilés, J.M. et al. JAMDA, 2016

HMB: Ergogenic Nutritional Supplement

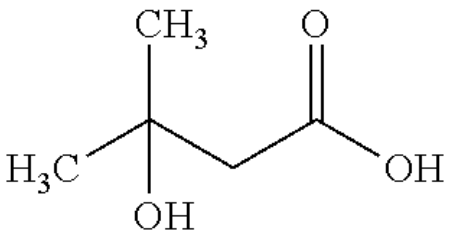


Leucine metabolite

Grapefruit, alfalfa, catfish

β-Hydroxy-β-Methylbutyrate (HMB)

- **HMB is a natural metabolite of the amino acid leucine[1]**
  - Produced in low levels in the body



- **Science behind HMB**
  - Originated in the 'Sports Nutrition ' world
  - Studied in relation to disease states and older adults for over 15 years[2]
  - Ca-HMB is Generally Recognized As Safe (GRAS) up to 6 g/day

Most referenced dose 3 g/d (Ca-HMB), no safety issues [1,2,3]

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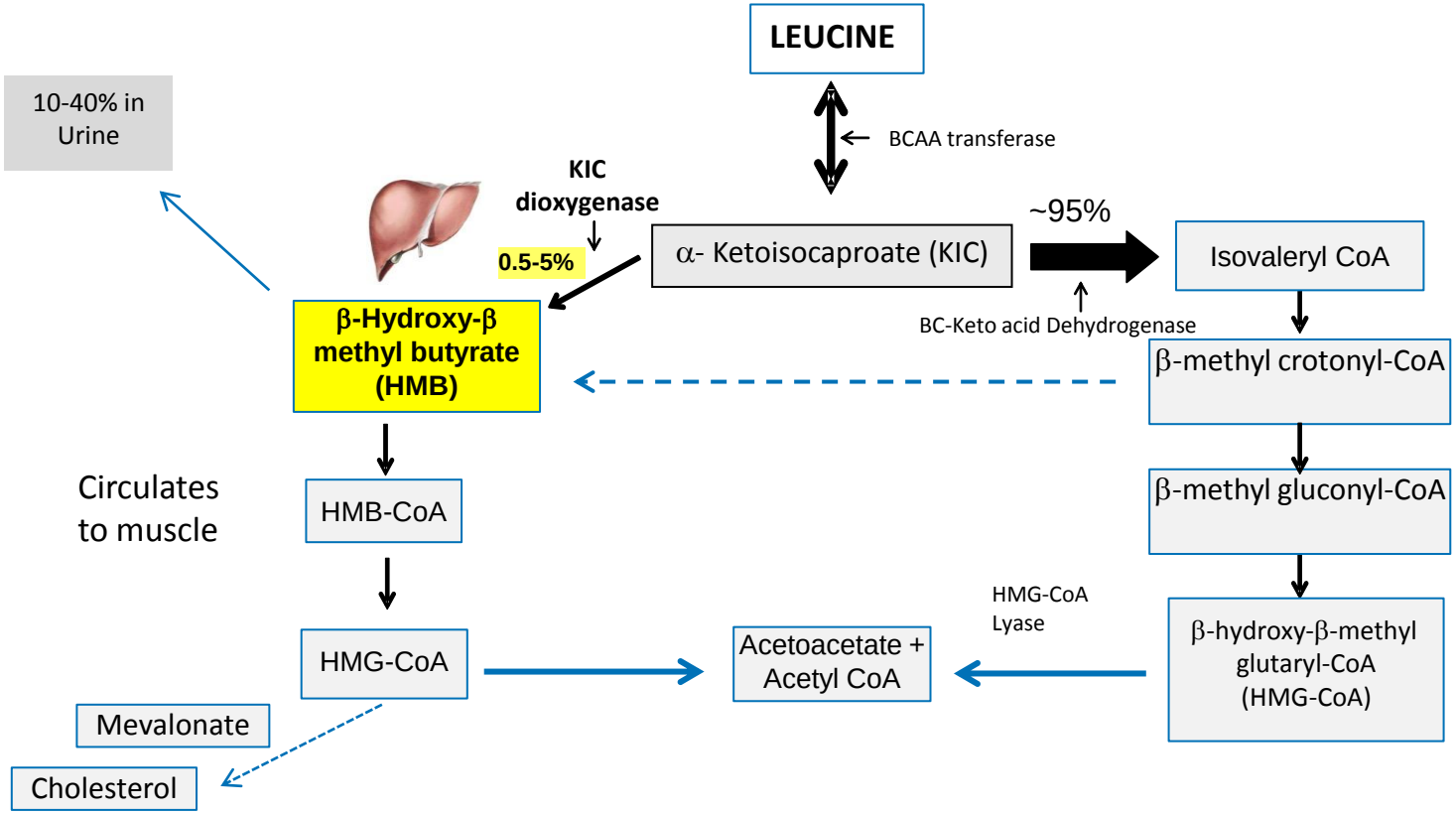
1. Nissen SL, Abumrad NN. *J Nutr Biochem*. 1997;8:300-11
2. Wilson GJ et al *Nutr Metab*. 2008;5:1 (review)
3. Fitschen, PJ. et al. *Nutrition* 29.1 (2013): 29-36.

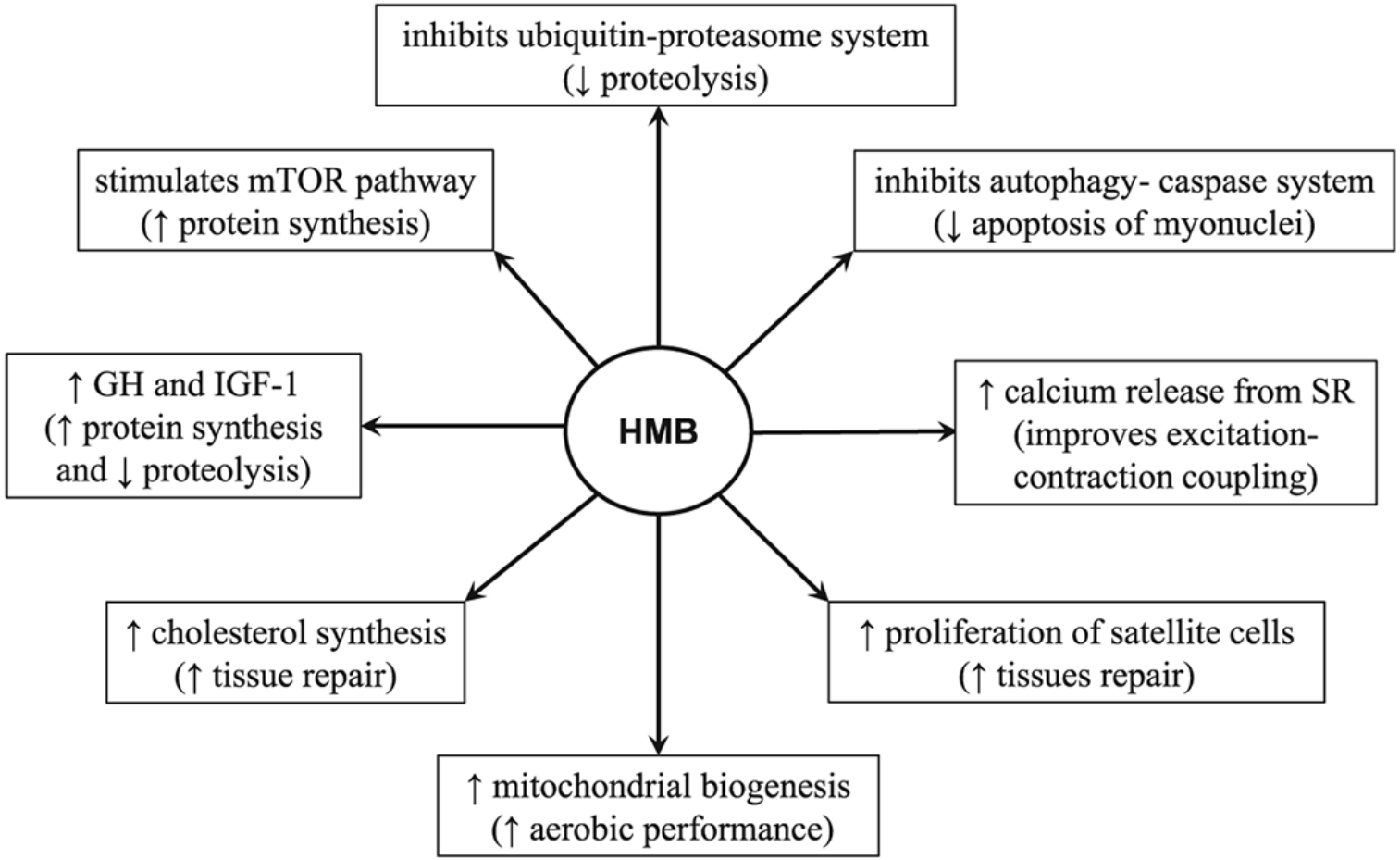
Metabolism of HMB in the Body



Sabourin,PJ and Bieber LL . *Metabolism* 32.2 (1983): 160-164.
Nissen SL, Abumrad NN. *J Nutr Biochem*. (1997);8:300-11.
Walker D et al *J. Chromat. B* 1040 (2017): 233-238.

Mechanisms

β-hydroxy-β-methylbutyrate supplementation and skeletal muscle in healthy and muscle-wasting conditions



Holecek, M. J. Cachexia Sarc. Muscle., 2017

Developing Muscle Wasting (Atrophy)-Specific Nutritional Approaches

Objectives

→ Increase body weight
Stimulate food intake

→ Decrease inflammation
Decrease energy expenditure

→ Enhance absorption/Gastric emptying
Preserve LBM (anabolic + anticatabolic)

→ Enhance QoL
Control disease
Increase survival

Take Home Messages

Skeletal Muscle as a metabolic organ	• Skeletal Muscle:
	  • Orchestrates metabolic events
	  • Regulates metabolic homeostasis
	  • Serves as an important thermogenic, metabolic, and endocrine organ

Skeletal Muscle wasting in disease	• Skeletal Muscle wasting is associated with morbidity and mortality
Nutrition and Skeletal Muscle wasting	• Conventional nutrition is unable to reverse muscle wasting • Use of drugs is associated with toxicity
Nutraceuticals: HMB	• Combination of nutritional approaches (including nutraceuticals) with exercise has important potential in treatment of muscle wasting • HMB: ↑ body weight, stimulates food intake, ↓ inflammation, and may serve to preserve LBM